ATTENTIONAL BIAS TO PAIN-RELATED INFORMATION: A META-ANALYSIS

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ABSTRACT

This meta-analysis investigated whether attentional bias, i.e. the preferential allocation of attention to information that is related to pain, is a ubiquitous phenomenon. We also investigated whether attentional bias effects are related to the methodological quality of the study, to procedural differences in their measurement, or to individual differences in pain severity, pain-related fear, anxiety and depression. Results indicated that individuals who experience chronic pain (n=1023) display an attentional bias towards pain-related words or pictures, but this bias was of a small effect size (d=0.134), and did not differ from that in control groups (d=0.082; n=1398). No evidence was found for an attentional bias towards pain-related words and pictures for acute pain (d=0.049), procedural pain (d=0.142), and experimental pain (d=0.069). However, research in which attentional bias towards signals of impending experimental pain in healthy volunteers was investigated, revealed an attentional bias of medium effect size (d=0.676). Moderator analyses in the chronic pain group identified important procedural variables that affected the presence and magnitude of an attentional bias towards pain-related words and pictures, i.e. type and exposure time of pain-related information. None of the individual difference variables affected the magnitude of the attentional bias. Implications of current findings and future directions are discussed.

1. INTRODUCTION

Attending toward, dwelling upon, and switching away from pain, have emerged as core components of many cognitive-affective models that seek to explain pain, distress and disability [45,77,154]. Particularly influential is the idea that patients selectively attend to pain at the cost of other information in the environment. This idea has been variably discussed as somatosensory amplification [12,98], hypervigilance [23,35], and more recently as attentional bias [81,120,129,135].

The concept of attentional bias was originally introduced by information processing accounts of psychopathology [13,47,92,103]. Attentional bias, or preferentially attending to information that is related to the content of the emotional concerns of patients, has proven to be a robust phenomenon in many forms of psychopathology [21,25,50,117,165]. For example, patients with phobic and anxiety disorders display an attentional bias to threat-related words or pictures [11]. In many of these models biased information processing is not considered epiphenomenal, but instead is invoked as a predisposing, initiating, exacerbating, or maintaining feature of the disorder [11,58,93]. Although much research is correlational, some longitudinal and interventional studies support these accounts [58].

Attentional bias to pain-related information is also the subject of significant research activity in pain [4,9,81,120,154,157]. Pain researchers have typically adopted hypotheses and paradigms from psychopathology research. In the first study on this topic, Pearce and Morley (1989) adapted the modified Stroop task, and presented pain patients with cards containing colored words [116]. They instructed participants to name the color of the words while ignoring word meaning. In comparison with control subjects, patients were slower in naming the color of pain-related words than in naming the color of neutral or more general, negative affective words. This was taken as evidence that chronic patients display an attentional bias towards pain-related information. However, further studies showed attentional bias to be a subtle phenomenon, and reported variable success in replicating this early finding [7,32,129].

A meta-analytic synthesis is necessary because in combining data from multiple studies we can overcome the restrictions or peculiarities of any singular study [22]. Reviews on this topic have been reported, but are early reviews [120,129] or are narrowly focused [129,135]. Here, we provide a broad, integrative meta-analysis on attentional bias. We investigate whether a stable bias of attention to pain-related information exists when people behave in a context of pain or threat of pain. We also investigate whether

attentional bias effects are related to the methodological quality of the study, to procedural differences in its measurement, or to individual differences in pain severity, pain-related fear, anxiety and depression.

2. METHODS

2.1. Literature search

Studies were identified through a search of electronic databases (MEDLINE, PsychINFO, Web of Science), using the following keywords: *selective attention*, attention* bias*, vigilance, hypervigilance, Stroop, dot probe, probe detection, Posner, spatial cueing or spatial cuing*, intersected with *pain*. In addition, the references of relevant review articles [120,129] were searched for additional relevant studies. Also, senior researchers in the area were invited by email to check our list of studies, and to provide references of missing studies.

2.2. Inclusion criteria

The following criteria were used to select studies for inclusion in the meta-analysis:

1. The study was a full report published or in press as a journal article in the English language.
2. The study sample consisted of adults, or the mean age of the sample was at least 18 years.
3. The study included a group of participants for whom pain was a current or salient concern, and/or included participants for whom pain was not a current concern. For pain groups, we included studies with individuals who experience pain in daily life (acute pain group and chronic pain group), individuals who experience or anticipate experiencing pain because of medical procedures (procedural pain group), and individuals who experience or anticipate experiencing pain within the context of an experimental study (experimental pain group). Groups were excluded from the meta-analyses whenever participants were selected on a psychiatric disorder rather than a pain disorder. We also included data of all possible groups for whom pain was not a current or salient concern. These were considered as control groups. Finally, although some studies with healthy volunteers investigated the role of individual difference variables (such as pain catastrophizing or fear of pain) on attentional bias, we coded these groups as

control groups whenever the experimental procedure did not reveal any information that individuals were currently concerned about pain (e.g., experienced pain or anticipated pain in the experimental context).

4. The study used a behavioural measure of attentional bias using paradigms in which the processing of pain-related information is irrelevant to the task at hand [35]. This was the case for the following experimental tasks: the modified Stroop task, the dot-probe task, and the modified spatial cueing task.
5. Studies compared responses to pain-related stimuli with responses to neutral stimuli on a within-subject basis. Possible effects are therefore unlikely to be related to general effects such as the slowing down of information processing [53,105].
6. Studies assessed attentional bias towards pain-related information, and not towards pain itself. In so doing, the focus of our meta-analysis remains in line with reviews and theoretical articles of attentional bias in anxiety [11]. This limitation will facilitate comparison with findings of attentional bias in fear and anxiety.
7. We excluded studies that used data reported in other articles for secondary analyses (e.g. [6,40].
8. Data allowing the computation of effect sizes were available. All authors were contacted to provide the original data, which were used for computation. If original data were not available, the data provided in the article were used. If the effect size could not be calculated, the study was excluded (e.g., [116]).

The electronic databases were searched for references on the 14th of October 2010 and resulted in 1138 references. A two-step procedure was used. In a first step two reviewers independently screened the abstracts of studies for possible inclusion. Reviewers were not blind for authors, institutions, journals and results. There were some disagreements between the reviewers (kappa = .83), but most concerned studies for which the abstract raised doubts about exclusion. Consensus was used to resolve disagreement. This resulted in 97 references. In a second step, full copies of articles were obtained and read. After reading the full copies 46 articles, reporting a total of 50 independent studies, were considered eligible for the analysis. Figure 1 provides the details of the results of our search procedure, and the main reasons for the exclusion of publications.

Figure 1 about here

2.3. Coding system and coding decisions

We used a standard coding system to rate every study in terms of both study and sample characteristics, in terms of methodological quality (see Table 1), in terms of its experimental procedure (see Table 2), and in terms of the self-report instruments to measure individual differences in pain severity, pain-related fear, state and trait anxiety and depression (see Supplementary table 3). The coding categories were developed iteratively. We requested authors of selected articles to provide us with the original data files. This allowed us to identify overlapping participants in studies, combining data of subgroups when needed, to check for possible statistical errors, to calculate effect sizes on all available information, and to calculate the effect of individual differences upon attentional bias. Whenever there was uncertainty, we contacted authors for clarification. Thereafter, the coding system was finalized by the authors.

For study characteristics we coded journal name, year of publication, experimental design (i.e. within- subjects design [e.g. 32], within- and between-subjects design [e.g. 7]) and its category in the Web of Science database. For sample characteristics, we coded sample size (*n*), mean age of participants, percentage female, and type of pain involved (Type of pain: i.e. chronic pain, procedural pain, experimental pain, acute pain).

The coding system for the methodological quality of the studies related to the internal validity, i.e. the extent to which a study allows for cause-effect inference, and the external validity, i.e. the extent to which a study allows for a generalization of the findings to other relevant settings and samples. Setting criteria for internal and external validity is a hazardous enterprise, and open to debate and discussion. A minimum guarantee for the internal and external validity was already set by our inclusion criteria. There are, however, many other threats to internal and external validity [61], and these are often difficult to assess in publications. For example, when no information is available on a particular criterion, one is unable to judge whether the authors have considered this criterion but failed to report it, or whether it concerns a real threat to the validity of the study. We decided to base our assessment on the information as provided by the study report. In line with the philosophy of the CONSORT criteria [101], we considered that authors should report information regarding critical features of their methods and results to allow readers to make inferences regarding the internal and external validity of the

study. Although Consort criteria are guidelines for the conduct and reporting of randomized controlled trials, many of the biases they address are relevant for experimental studies. More specifically, we selected guidelines related to the internal and external validity, and, where necessary, adapted them to the particular context of attentional bias research. Criteria for external validity were related to the description of the following features of the study: eligibility criteria, participant demographics, pain experience in pain and control groups, recruitment procedure, setting and/or location of the study, and data cleaning. Criteria for internal validity were related to the description of the following features in the study: selection and relevance of any pain-related stimuli, matching of non-pain related stimuli to the pain-related stimuli, and engagement of participants with the task. Criteria for external validity were coded at the level of the study. Criteria for internal validity were first coded at the level of conditions, and subsequently averaged to obtain one index per independent study.

The coding of the characteristics of the experimental procedures was based upon that of Bar-Haim et al. (2007) who performed a meta-analysis of attentional bias to threat-related information in anxious and non-anxious individuals [11]. We coded the type of paradigm used (Type of paradigm: modified Stroop task, dot-probe task, modified spatial cueing task), and the type of stimuli in the paradigm (Stimulus type: pictures, words or predictive cues for pain). We also coded whether stimuli in the modified Stroop task were presented in block (i.e. stimuli of different categories in separate blocks) or randomly. To assess the effect of stimulus exposure we coded whether stimuli were presented subliminally or supraliminally (Stimulus exposure: subliminal, supraliminal). In line with Bar-Haim et al. (2007) we further specified the stimulus exposure times for the dot probe task and modified spatial cueing task (subliminal, <500ms, 500-1000ms, >1000ms) [11]. Finally, we took into account the type of stimulus material used. According to a previous meta-analysis of modified Stroop studies in pain research [129], we made a distinction between stimulus material that described the sensory qualities of pain (e.g., words like “stabbing”, “burning”) and stimulus material that described the affective component of pain (e.g., words like “annoying”, “terrifying”). There were three extra categories. Stimulus material could relate to contextual elements that often precede or coincide with the experience of pain (antecedents; e.g., words like “wound, “blood” and “fall”), or could relate to consequences that are often associated with experiencing (chronic) pain (consequences; e.g., words like “disability”, “disable” and “wheelchair”). As it emerged that some studies used stimuli belonging to several categories, we finally created a

category "mixed" when less than 50% of the words belonged to one of the specified categories (Type of pain-related information: i.e. sensory quality, affective quality, antecedents, consequents, mixed).

Because we expected that individual difference variables would affect attentional bias, we also coded whether studies included individual difference variables in relation to pain severity, pain-related fear, state anxiety, trait anxiety and depressive mood. A summary of the most frequently used instruments is provided in Supplementary table 3.

Some additional data-extraction and coding decisions were made. First, when studies involved a clinical treatment (or a manipulation), we only selected the data from the pre-test measurement (e.g. [89]) Second, when a study did not report the overall results for a group of interest, but reported subgroups (e.g., group of high and low pain-related fear), the first option was to compute the overall result. If, however, the authors could not provide the original data, we treated the data subgroups as independent groups.

Data-extraction and coding was conducted by two reviewers (DVR & SVD) using a form specifically designed for this meta-analysis. If necessary, a third reviewer (GC) was asked to resolve disagreements. The final coding reflected the consensus of the coding. Inter-coder reliability was established on all studies included in the meta-analysis. Kappa's ranged from .63 to .88 (see Table 1).

Table 1 about here

2.4. Meta-analytic procedures

We were able to retrieve 82% of the original data, and therefore we recalculated the indices of attentional bias where possible. In a first step, an attentional bias index and its standard deviation was calculated or identified for each condition. Essentially, attentional bias indices involve a within-subject difference between two means, albeit with some differences according to the type of procedure. The modified Stroop task is an adaptation of the classic Stroop task [141] in which participants are instructed to identify the ink color of presented color words, while ignoring the meaning of the words. In the modified Stroop version, the color words are replaced by emotionally valent, often threat related, words and neutral words [161]. In pain research, the threat-related words consist of pain-related words [116]. Participants are instructed to identify as fast as possible the color of the word, while ignoring the meaning of the word. Biased attention for pain-

related information is inferred when color naming of the pain-related words (mean 1) is slower or less accurate compared to neutral words (mean 2).

The dot-probe task was developed to measure attentional bias towards threat-related information [85]. In this task, two cue stimuli are simultaneously presented on different spatial locations on a computer screen. One of these cues is threat-related, whereas the other cue is neutral. After a short interval, the cues disappear and a target probe (often a dot) appears in one of the two previously cued locations. In pain research the threat-related cue is replaced by pain-related information [7]. The pain-related cue may consist of words or pictures. Participants are instructed to respond as fast and as accurately as possible to the location or the identity of the target. An attentional bias towards pain-related stimuli is inferred from faster reaction times on trials where the target appears on the same spatial location as the pain-related cue (congruent trials; mean 2) relative to reaction times on trials where the target appears on the location of the neutral cue (incongruent trials; mean 1).

The modified spatial cueing task is an adaptation of the cueing task of Posner (1980) [122]. A single cue stimulus, which is either threat-related or neutral, is presented at one of two possible locations. After a brief interval, the cue disappears and a target appears either at the previously cued location (congruent trials), or at the opposite location (incongruent trials). In half of the trials the cue is threat-related [52]. In pain research, the threat-related cue is replaced by a pain-related cue [150]. Participants are instructed to respond as quickly and as accurately as possible to the identity or the location of the target. A cue validity index is computed by subtracting reaction times on congruent trials from reaction times on incongruent trials. Attentional bias towards pain-related information is indicated by a greater cue validity index on trials with a pain-related cue (mean 1) compared to trials with a neutral cue (mean 2).

The effect size index in our meta-analysis was either the standardized paired difference (Cohen's *d* for paired data) [106], or the correlation coefficient (*r*) [131]. Cohen's *d* was used to investigate whether an attentional bias exists for those who are currently concerned with pain, and whether attentional bias varies as a function of particular groups or conditions. Here, groups and conditions are categorical variables. The standardized paired differences were calculated by dividing the attentional bias index of each study condition by its standard deviation. In the calculation of the standardized paired difference, the correlation between the two means used to calculate the attentional bias index was computed from the original data. In cases where the correlation could not

be computed, we calculated and imputed the correlation for each type of experimental paradigm using a meta-analytic approach of the available correlations. The imputed correlation between the two means for the modified Stroop task was .89 (95% CI [.85: .92], *k*=23; *n*=869), for the dot-probe task it was .90 (95% CI [.86: .92], *k*=29; *n*=1909), and for the modified spatial cueing task it was .55 (95% CI = [.43: .65]; *k*=8; *n*=290). Standardized paired differences (*d*) with a positive sign indicated an attentional bias towards pain-related information, whereas effect sizes with a negative sign indicated an attentional bias away from pain-related information.

We used the correlation coefficient (*r*) as an effect size index to summarize the effect of continuous variables upon attentional bias. These continuous variables were from self-report instruments that assessed individual differences in pain severity, pain-related fear, state anxiety, trait anxiety, and depression. For each measure in a study, we calculated the correlation coefficient between the individual scores on that measure and the corresponding attentional bias. Correlation coefficients with a positive sign indicated that an increasing score on a continuous measure was related to a larger attentional bias towards pain-related information, whereas correlation coefficients with a negative sign indicated that an increase on a continuous measure was related to a smaller attentional bias.

In our meta-analyses we took into account the sampling error of each sample. Effect sizes were weighted by the inverse of the estimated sampling variance of the corresponding effect, whereby high-precision effect sizes gain more weight than low-precision estimates. For all analyses we chose a mixed effects model. We applied Cochran's *Q* test to judge the degree of heterogeneity in effect sizes [18]. To address whether variations in effect sizes can be explained by categorical coded variables, we performed moderator analyses, which can be considered as a meta-analytic ANOVA analog. Variance in effect sizes is partitioned into the portion explained by the categorical variable (Q_B) as an indicator of variability between group means and the residual remaining portion (Q_W) as an indicator of variability within groups. A significant between-groups effect indicates that the variance in effect sizes is at least partially explained by the moderator variable. To maintain the independence of our data, whenever necessary, we averaged effect sizes across conditions. When this turned out not to be possible, we selected the data from that condition that had the least participants. Finally, for the continuous coded variables (e.g. internal and external validity score), we performed meta-regressions using the Methods of moments procedure [145]. The

outcome of this meta-regression is reported as a point estimate of the slope. All our analyses and computations were carried out using Comprehensive Meta-Analysis software, Version 2.2.050 (Biostat, Englewood, NJ).

Fifty studies (177 conditions reported in 46 publications met our initial inclusion criteria, and were included in the meta-analysis. Screening the entire data set for outliers revealed two conditions from two different studies that yielded an effect size that differed more than 3 *SD* from the corresponding group mean. In the study of Khatibi and colleagues (2009) using the dot-probe task, the effect size for the control condition using pictures displaying faces was an outlier (> 3 *SD* under group mean) [69]. In the study of Pincus and colleagues (1998) using the modified Stroop task, the effect size for the condition using words reflecting the affective quality of pain in individuals with chronic pain was an outlier (> 3 *SD* above group mean) [119]. Therefore, our meta-analysis is based on a total of 50 studies reported in 46 publications. Effect sizes were available for 76 independent groups (35 control groups, 41 pain groups) and for a total of 175 conditions.

3. RESULTS

3.1. Descriptive statistics and methodological quality

There were 22 studies with the modified Stroop task, comprising of 36 independent groups (19 control groups, 17 pain groups; 73 conditions). There were 23 studies with the dot-probe task, comprising of 34 independent groups (15 control groups, 19 pain groups; 92 conditions), and there were 6 studies with the modified spatial cueing task, comprising of 8 independent groups (2 control groups, 6 pain groups; 10 conditions). There was one study [10] that reported the results of the modified Stroop task and the dot-probe task from the same participants. Of the 50 studies, 12 were within-subject designs and 38 were within- and between-subject designs.

The average sample size for the pain groups (chronic pain, acute pain, procedural pain and experimental pain) and the control groups was respectively 50 (*SD*=5, *N* total=2035) and 40 (*SD*=29, *N* total=1398). Number of studies, conditions, and samples sizes varied substantially as a function of type of pain. In the chronic pain group there were 23 studies (25 independent groups), with a total sample size of 1023 participants. In the experimental pain group there were 12 studies (12 independent groups), with a total sample size of 803 participants. In the procedural pain group, there were only 3 studies (3

independent groups), with a total sample size of 161 participants. In the acute pain group, there was only one study (n = 51). Most studies were published in the Web of Science category "Clinical Neurology" (29), followed by "Neurosciences" (27) and "Anesthesiology" (21). Most studies were published in the journals "Pain" (11), "The Journal of Pain" (8) and "European Journal of Pain" (8).

On average studies fulfilled 69.88% (SD=21.47) of the external validity criteria and 57.23% (SD=22.36) of the internal validity criteria that are applicable for the study (see Table 1). Of note, analyses revealed that the scores on the validity criteria increased with publication year, indicating that authors are increasingly reporting more details of their study (external validity: r=.32; internal validity: r=.54). However, it is clear that there is still room for improvement.

3.2. Rationale for (sub) grouping

Before performing the moderator analyses, we describe here the rationale for performing separate analyses and for grouping participants. As is often the case, some of these were anticipated, but others were not. We suspected that large differences in effect sizes would exist between studies that used symbolic representations of pain or associated events (i.e. pictures or words) and studies that used predictive cues of impending pain, and so decided to analyze this effect before performing proper moderator analyses. This decision was made for several reasons. First, if large differences exist, it may be wise to keep studies with predictive cues apart from the other studies. These studies investigating attentional bias towards predictive cues for pain have similar sample and procedural characteristics. When investigating other moderator variables they may then be confounded by this background variable. Second, the meta-analysis of Bar-Haim and colleagues (2007) only included studies with symbolic representations of threat [11]. By keeping studies with predictive cues apart from the other type of studies, the comparability between the two meta-analyses increases. Therefore, we tested whether there were substantial differences in effect size between the types of stimulus (i.e. words, pictures or predictive cues). As expected, the effect size for the attentional bias towards predictive cues of pain (d=0.673) was significantly larger than the effect size for both the attentional bias towards words, d=0.112, Q(1)=13.455, p<.001, and pictures, d=0.045, Q(1)=10.238, p<.001. Noteworthy was that the difference in effect size between words and pictures was not significant, Q(1)=0.199. We decided therefore to keep the data relating to the predictive cues of pain apart, and to analyze them in a separate section.

We combined all control groups. This approach differs from the meta-analysis of Schoth et al. (2012) who only included studies in which both a chronic pain group and a control group were present [135]. An advantage of a matched control group is that the procedural features are identical for the pain and the control group. A disadvantage, however, may be an increased opportunity for publication bias: Studies that did not observe differences between groups are more difficult to publish. The advantages of including all possible control groups are that (1) analyses are based upon the maximum available evidence, thereby increasing statistical power, and (2) publication bias is less of an issue. A disadvantage may well be that control groups differ and may not be aggregated. For that reason we tested whether effect sizes differed between our different types of control groups. In total we had data from 35 control groups, belonging to 13 control groups not matched to a pain group (n=861), 18 control groups matched to a chronic pain group (n=431), 1 control group matched to both an acute and chronic pain group (n=50), 2 control groups matched to an experimental pain group (n=40), and 1 control group that was matched to a procedural pain group (n=16). Effect sizes between these types of control groups were not significant, $Q(4)=4.981$, $p=0.29$. So, in our between-group analyses we compared effect sizes of our pain groups with the combined control groups.

3.3. Attentional bias to pain-related words and pictures: the effect of groups

We provide the effect sizes (d), 95% Confidence Intervals (95% CI), number of independent groups (k) and number of participants (n) for the chronic pain groups, the acute pain group, the procedural pain groups, experimental pain groups, and the control groups. The effect size for the attentional bias in the chronic pain groups (k=25, n=1023) was small but significant (d=0.134, 95% CI [0.045: 0.223], p<.01). There was substantial heterogeneity ($Q(24)=39.927$, p<.05), warranting further moderator analyses. The effect size for the experimental pain groups (k=8, n=624) was not significant (d=0.069, 95% CI [-0.017: 0.154]) with no evidence for heterogeneity ($Q(7)=8.065$). The effect size for the procedural pain groups (k=3, n=161) was not significant (d=0.142, 95% CI [-0.118: 0.401]), also with no significant heterogeneity ($Q(2)=5.013$). There was only one study that included patients experiencing acute pain (n=51) [57]. The effect size was not significant (d=0.049, 95% CI [-0.236: 0.333]). Finally, the effect sizes for attentional bias in the control groups (k=35, n=1398) was also not significant (d=0.082, 95% CI [-0.007: 0.171]), but there was substantial heterogeneity ($Q(34)=83.857$, p<.001).

In sum, an attentional bias towards pain-related information is present in the chronic pain group but not in the other pain groups. However, a between-group analysis indicated that there was no significant difference between these groups ($Q(4)=1.388$). Because there was no significant heterogeneity in the effect sizes for the acute pain group, the procedural pain groups and the experimental pain groups, we decided not to perform a moderator analyses for these groups. Hence, the following analyses are performed only on the chronic pain groups and the control groups.

3. 4. Attentional bias to pain-related words and pictures in chronic pain and control groups: the effect of internal and external validity

We investigated whether attentional bias to pain-related information in the chronic pain groups and in the control groups varied as a function of the external and internal validity of the studies. A meta-regression revealed that the attentional bias effect sizes (*d*) in the chronic pain groups was not influenced by the internal validity score of the studies, point estimate of slope=0.247, 95% CI [-0.114: 0.607], nor by the external validity score of the studies, point estimate of slope=-0.010, 95% CI [-0.514: 0.495]. The effect size for attentional bias in the control groups was significantly affected by the internal validity score, point estimate of slope=-0.489, 95% CI [-0.860: -0.119], $p<.001$, and by external validity score, point estimate of slope=-0.617, 95% CI [-1.087: -0.147], $p<.05$). The greater the internal and external validity scores of studies, the smaller the attentional bias index in control subjects.

3.5. Attentional bias to pain-related words and pictures in chronic pain and control groups: the effect of procedural characteristics

Table 2 provides the effect sizes (*d*), 95% Confidence intervals, number of independent groups (*k*) and number of participants (*n*) for the chronic pain groups and the control groups as a function of key procedural characteristics of the paradigms used.

Does attentional bias to pain-related words and pictures differ according to the paradigm used? Most often the dot probe task ($k=12$, $n=734$) and the modified Stroop task ($k=12$, $n=272$) have been used. Only recently has the spatial cueing task been adopted for research in pain patients ($k=2$, $n=53$) [24,89]. The effect size for attentional bias in the chronic pain groups was not significant for the dot probe task ($d=0.091$) and for the modified spatial cueing task ($d=0.222$). There was a significant effect for the modified Stroop task ($d=0.168$, $p<.05$). None of these effect sizes differed from the effect

sizes of the control groups. In a further analysis we explored whether the effect sizes for attentional bias in the chronic pain groups differed according to the paradigm used. There was no significant difference in detecting attentional bias as a function of paradigm used in the chronic pain groups ($Q(2)=1.007$).

Does attentional bias to pain-related information differ when stimuli are presented in block or randomly in the modified Stroop task? An intermixed and random presentation of stimuli did not result in a significant effect in the chronic pain groups **(***d*=0.087**)**, and in the control groups **(***d*=0.037**)**. Noteworthy is that a blocked presentation of the stimuli resulted in a significant effect size, and this was for both the chronic pain groups **(***d*=0.341, *p*<.05**)**, and the control groups **(***d*=0.404, *p*<.05**)**. Between-group analyses revealed that the effect sizes did not differ between chronic pain groups and control groups both for the blocked presentation **(***Q*(1)=0.085**)**, and for the random presentation **(***Q*(1)=0.173**)**. In a final series we investigated whether attentional bias in the chronic pain groups differed when presentation of stimuli was blocked or random. This was the case **(***Q*(1)=5.194, *p*<.05**)**. This effect was also significant for the control groups **(***Q*(1)=5.183, *p*<.05**)**. A blocked presentation of stimuli in the modified Stroop task resulted in a larger attentional bias than a random presentation of stimuli.

Does attentional bias to pain-related information differ when pain-related information consists of words or pictures? The use of pictures as pain-related information is relatively recent in pain research. There were only 3 independent studies (*k*=3; *n*=236) in the chronic pain groups and in the control groups (*k*=3; *n*=111). All of them used the dot-probe task. The effect size in the chronic pain groups was not significant when pictures as cue stimuli were used (*d*=0.045), whereas a significant effect was present when words as stimuli were used (*d*=0.148, *p*<.01). The effect sizes in the control groups did not reveal any significant effects for pictures or words as stimuli. There were no significant differences in effect sizes between the chronic pain groups and the control groups both for pictures as stimuli (Q(1)=0.038), and for words as stimuli (Q(1)=0.922). Finally, we investigated whether attentional bias using pictures differed from attentional bias using words. For the chronic pain groups there was no significant difference in the effect size between pictures or words as stimuli (Q(1)=0.874). For the control groups there was also no significant difference (Q(1)=0.067).

Does attentional bias to pain-related information differ as a function of stimulus exposure? The issue whether attentional bias to pain-related information exists when stimuli are subliminally presented, has not attracted a lot of research. There are only two

independent studies [10,138] with a total of 69 chronic pain patients, and four independent studies [10,67,80,138] with a total of 176 control participants. The effect size for subliminally presented pain-related information was not significant in the chronic pain groups **(***d*=-0.174**)** as well as in the control groups **(***d*=-0.258**)**. The effect size for stimuli that were supraliminally presented was significant in the chronic pain groups **(***d*=0.149, *p*<.01**)**. This was not the case in the control groups **(***d*=0.088**)**. The effect sizes for subliminally presented stimuli did not differ between the chronic pain groups and the control groups **(***Q*(1)=0.171**)**. There was also no significant difference between the chronic pain groups and the control groups for supraliminally presented stimuli **(***Q*(1)=0.875**)**. Finally, we investigated whether supraliminally presented stimuli resulted in larger attentional bias than subliminally presented stimuli. Supraliminally presented stimuli resulted in a larger effect size for attentional bias than subliminally presented stimuli in the chronic pain groups **(***Q*(1)=6.012, *p*<.05**)** as well as in the control groups **(***Q*(1)=5.141, *p*<.05**)**.

In contrast with the modified Stroop task, the dot-probe paradigm and the modified spatial cueing paradigm allowed for a more detailed investigation of the time course of attentional bias when pain-related information was presented supraliminally. Regarding chronic pain groups, we identified 3 groups (*n*=364) that were presented pain-related information with a duration between 100 ms and 500 ms, 12 groups (*n*=597) that were presented pain-related information between 500 ms and 1000 ms, and 3 groups (*n*=72) that were presented stimuli longer than 1000 ms. For the chronic pain groups, the effect sizes were not significant for a stimulus presentation less than 500 ms (*d*=0.082) and for a stimulus presentation between 500 and 1000 ms (*d*=0.077). The effect was significant when stimuli were presented for longer than 1000 ms (*d*=0.723, *p*<.001). For the control groups, the effect size was significant for a stimulus duration lasting less than 500 ms (*d*=-0.316, *p*<.01). Noteworthy is that this effect indicated that participants directed attention away from instead of towards pain-related information. The effect sizes of the control groups were not significant for a stimulus presentation between 500 and 1000 ms, (*d*=0.064), and for a stimulus presentation longer than 1000 ms (*d*=-0.150). There was a significant difference between the chronic pain groups and the control groups for the presentation duration of less than 500 ms (*Q*(1)=5.183, *p*<.05). There was no difference between the chronic pain groups and the control groups for a stimulus presentation between 500 ms and 1000 ms (*Q*(1)=0.047). This difference between the chronic pain groups and the control groups was again significant for a stimulus duration

longer than 1000 ms ($Q(1)=16.658$, $p<.01$). In a final analysis we investigated whether attentional bias differed as a function of stimulus exposure. For the chronic pain groups, there was a significant difference in the effect size between the different durations of stimulus exposure ($Q(2)=22.685$, $p<.001$). For the control groups, there was also a significant difference ($Q(2)=14.285$, $p<.001$).

Does type of pain-related information affect attentional bias? The seminal paper of Pearce and Morley (1989), in which the authors wanted to validate the sensory and affective pain dimensions of the McGill Pain Questionnaire using the modified Stroop task has inspired many researchers to use and select similar stimulus material [116]. For the chronic pain groups, 18 independent groups ($n=731$) were presented words that reflect sensory characteristics of the pain experience, and 11 independent groups ($n=554$) were presented words that reflect the affective characteristics of pain. Nine independent groups ($n=665$) were presented stimulus material that could be classified as possible consequences of pain (e.g. the words "inactive" and "disable"; [57]). There were 7 independent groups ($n=186$) that were presented stimulus material we classified as possible antecedents of pain (e.g. the words "accident" and "fracture"; [160]). The effect size for words representing the sensory quality of pain was significant in the chronic pain groups ($d=0.316$, $p<.001$), but not in the control groups ($d=0.016$). The effect size for stimuli that represent the affective quality of pain was not significant in the chronic pain groups ($d=0.083$), and in the control groups ($d=0.084$). The effect size for stimuli that represent possible antecedents of pain was significant in the chronic pain groups ($d=0.160$, $p<.05$). This was not the case in the control groups ($d=0.183$). The effect size for stimuli that represent possible consequences of pain was not significant in the chronic pain groups ($d=0.065$), and also not in the control groups ($d=-0.156$). The effect sizes for stimuli reflecting the sensory quality of pain differed between the chronic pain groups and the control groups ($Q(1)=18.655$, $p<.001$). However, there were no significant differences between the chronic pain groups and the control groups for stimuli reflecting the affective quality ($Q(1)=0.424$), for stimuli reflecting antecedents of pain ($Q(1)=0.034$), and for stimuli reflecting consequences of pain ($Q(1)=0.439$). In a final analysis we investigated whether type of information affected attentional bias. For the chronic pain groups the type of pain-related information significantly affected the strength of the attentional bias ($Q(3)=17.956$, $p<.001$). This was not the case for the control groups ($Q(3)=6.247$, $p=.10$).

Interim summary. The analyses indicate that an attentional bias to pain-related information is present in chronic patients, albeit small, and no different from the

attentional bias in control participants. As there was substantial heterogeneity, a moderator analysis was performed focusing upon potentially important procedural parameters. Most of these parameters did not matter. When significant effect sizes for the chronic pain groups were present, in most cases these appeared not to differ from those in the control groups. There were exceptions. The presentation duration of pain-related information seemed to have an effect, as there were some significant differences between the chronic pain groups and the control groups, although the pattern was not entirely consistent. We were, however, able to identify one important moderator, i.e. type of pain-related information. Attentional bias in chronic pain patients seems to be robust for words that reflect the sensory characteristics of pain. This effect size was small, but significant for the chronic pain groups, and it was also different from the one for the control groups. Furthermore, type of pain-related information did significantly affect the effect size for the chronic pain groups. Based upon these results we decided to perform a second series of moderator analyses, but now only with the conditions consisting of sensory pain words. There are two reasons for this. First, possible important moderator effects may have been left undetected because of our analytic strategy to average across conditions to keep data independent. This may have masked other effects. Second, heterogeneity analysis indicated that there was substantial heterogeneity in the effect size for sensory pain words in the chronic pain groups ($Q(17)=31.430$, $p<.05$). There was no indication of heterogeneity for the other types of pain-related information in the chronic pain groups.

Table 2 about here

3.6. Attentional bias to sensory pain words in chronic pain and control groups: the effects of internal and external validity.

A meta-regression analysis indicated that the effect size for attentional bias (*d*) in the chronic pain group was not significantly influenced by the internal validity score of the included studies, point estimate of slope=0.006, 95% CI [-0.430: 0.442], nor by external validity score of the studies, point estimate of slope=-0.336, 95% CI [-0.974: 0.302]. The effect sizes for attentional bias in the control group were also not significantly influenced by the internal validity score, point estimate of slope=-0.165, 95% CI [-0.573: 0.243], nor by external validity score, point estimate of slope=-0.388, 95% CI [-0.948: 0.173]. Of note, we were no able to replicate the findings in the control groups that attentional biases towards pain-related information (all types of pain-related words and pictures combined) became smaller with increasing internal and external

validity scores of the studies (see section 3.4). As yet, we have no explanation for these observations.

3.7. Attentional bias to sensory pain information in chronic pain and control groups: the effects of procedural characteristics

Does attentional bias to sensory pain words differ as a function of the paradigm used? The effect size of the chronic pain groups was significant for the dot-probe task (d=0.292, p<.001) and for the modified Stroop task (d=0.368, p<.05). The results for the modified spatial cueing task were not significant (d=0.222). However, there were only two independent studies with a total of 53 chronic pain patients. For the control group, there were no significant effect sizes. The effect sizes for the dot probe task, attentional bias to sensory pain words significantly differed between the chronic pain groups and the control groups (Q(1)=13.983, p<.01). The effect was similar, but not significant for the modified Stroop task, (Q(1)=3.018, p=.08) and the modified spatial cueing task, (Q(1)=2.823, p=.09). A final analysis indicated that there was no significant difference in detecting attentional bias to sensory pain words as a function of paradigm used in the chronic pain groups (Q(2)=0.594).

Does attentional bias to sensory pain words differ when stimuli are presented in block or randomly in the modified Stroop task? An intermixed and random presentation of sensory pain words did not result in a significant effect in the chronic pain groups (d=0.211), and in the control groups (d=0.055). Noteworthy is that a blocked presentation of the stimuli did result in a significant effect size for the chronic pain groups (d=0.600, p<.001), but not for the control groups (d=0.246). The effect sizes did not differ between chronic pain groups and control groups for both the blocked presentation (Q(1)=2.545), and the random presentation (Q(1)=0.651). Finally, we investigated whether attentional bias in the chronic pain groups differed when presentation of stimuli was blocked or random. The difference was not significant for the chronic pain groups (Q(1)=2.801, p=.09), or control groups (Q (1)=1.120).

Does attentional bias to sensory pain words differ as a function of stimulus exposure? The effect size for subliminally presented sensory pain words was significant in the chronic pain groups (d=-0.274, p<.05), but not in the control groups (d=-0.120). Noteworthy is that the effect size indicated that chronic pain groups directed attention away from sensory pain words. The effect size for sensory pain words that were supraliminally presented was significant in the chronic pain groups (d=0.341, p<.001).

This was not the case in the control groups (d=0.013).The effect sizes for subliminally presented stimuli did not differ between the chronic pain groups and the control groups (Q(1)=1.065). The difference between the chronic pain groups and the control groups for supraliminally presented stimuli was significant (Q(1)=23.205, p<.001). In a further analysis we investigated whether supraliminally presented sensory words resulted in larger attentional bias than subliminally presented sensory words. Supraliminally presented stimuli resulted in a larger effect size for attentional bias than subliminally presented stimuli in the chronic pain groups Q(1)=22.473, p<.001). This effect approached significance for the control groups (Q(1)=3.452, p=.06).

For the chronic pain groups, the effect size was not significant for a stimulus presentation less than 500 ms (d=0.240), but it was for a stimulus presentation between 500 ms and 1000 ms (d=0.247, p<.001), and for a stimulus presentation longer than 1000 ms, (d=0.698, p<.001). For the control groups, the effect size was significant for a stimulus duration less than 500 ms (d=-0.316, p<.01), indicating that participants directed attention away from instead of towards pain-related information. The effect sizes of the control groups were not significant for a stimulus presentation between 500 and 1000 ms (d=0.058), and for a stimulus presentation longer than 1000 ms (d=-0.225). Further analyses indicated that the effect sizes between the chronic pain groups and the control groups differed significantly for the presentation duration of less than 500 ms (Q(1)=11.433, p<.001), for the presentation duration between 500 ms and 1000 ms (Q(1)=5.647, p<.05), and for the presentation duration longer than 1000 ms (Q(1)=7.615, p<.01). In a final analysis we investigated whether attentional bias differed as a function of stimulus exposure. For the chronic pain groups, there was no significant difference in the effect size between the different durations of stimulus exposure (Q(2)=3.416). For the control groups, there was a significant difference (Q(2)=9.667, p<.01).

Interim summary. The results of the moderator analyses using only the conditions that used sensory pain words as pain-related information can be summarized as follows. Both the dot probe paradigm and the modified Stroop task revealed an attentional bias to sensory pain words in chronic pain patients, but an effect was not present with the modified spatial cueing task. Only for the dot probe task, the attentional bias to sensory information in chronic pain patients differed from that in the control participants. For the modified Stroop task and the modified spatial cueing task, this effect failed to reach a conventional level of significance. It may however be premature to conclude that the dot probe task is the most sensitive task. First, the analyses with the modified Stroop task and

with the modified spatial cueing task may have lacked statistical power. Second, we found no significant differences between the three attentional bias paradigms for the chronic pain groups. One further moderator was identified. It did matter whether sensory pain words were presented sub- or supraliminally. Only when sensory pain words were supraliminally presented did an attentional bias in chronic pain patients occur. When sensory pain words were subliminally presented chronic pain patients directed attention away from the sensory pain words, but this effect was no different from the one in the control groups. As yet, there is no evidence that time of stimulus presentation affects attentional bias once stimuli are presented supraliminally. All stimulus exposure categories revealed differences in effect sizes between chronic pain patients and control participants. Also, differences in stimulus exposure did not affect the attentional bias for the chronic pain patients.

3.8. Attentional bias to supraliminally presented sensory pain words in chronic pain: the effects of individual differences between patients

Chronic pain patients are heterogeneous, and it is reasonable to investigate to what extent individual difference between patients affect attentional bias in chronic pain. In our meta-analysis we focus upon individual differences in pain severity, pain-related fear, state anxiety, trait anxiety and depressive mood. There was a diversity in instruments used to assess individual differences. Overall, the classification of instruments was straightforward although some more sophisticated classifications were possible [63,108,147]. There were some difficulties in classifying the Anxiety Sensitivity Index (ASI). Anxiety Sensitivity is a fear of anxiety symptoms including thoughts and somatic sensations [123]. Recent psychometric analyses of various negative affect related measures relevant for pain have revealed the complex and multidimensional nature of the ASI items/subscales, but overall the ASI seems to be more related to pain-specific constructs than to general affect constructs [63,147]. For that reason we took the ASI as a pain-related fear measure.

The effect of Individual differences as continuous variables. For the moderator analysis investigating the role of individual difference variables upon attentional bias, we restricted the attentional bias data to the data relating to supraliminally presented sensory pain words in chronic pain patients. The reasons for selecting these data were as follows. First, most models discussing the role of attentional bias to pain-related fear attempt to explain pain and suffering in chronic pain patients. Second, the moderator analysis with

procedural parameters revealed that an attentional bias in chronic pain groups was only present for supraliminally presented sensory pain words. Third, chronic pain groups reliably avoided subliminally presented words,. Including these effect sizes may mask effects, especially when opposite effects of individual differences may emerge as a function of a type of stimulus exposure.

When possible, we calculated the correlation coefficients between the individual difference variable and the attentional bias index for each study using the data provided by the authors. In some cases, the original dataset was not available, but the correlation coefficients could be obtained from the publication. An outlier analysis revealed one outlier for the correlation coefficients using the McGill Pain Questionnaire-Present Pain Index [115].

There was a total of 89 correlation coefficients stemming from 14 independent groups. A mixed model meta-analysis was performed on the correlation coefficients. This analysis revealed no significant correlations between attentional bias and each of the five individual difference variables. The correlation coefficient for each of the five constructs was as follows: pain severity (r=-0.043, 95% CI [-0.134: 0.050; k=10, n=481), pain-related fear (r=0.031, 95% CI [-0.098: 0.158], k=10, n=438), state anxiety (r=-0.017, 95% CI [-0.101: 0.068], k=13, n=574), depressive mood (r=-0.051, 95% CI [-0.133: 0.031], k=14, n=609), and trait anxiety (r=0.013, 95% CI [-0.165: 0.190], k=6, n=150) (See Supplementary table 3). Effect sizes of this magnitude are considered negligible according to the guidelines of Cohen (1988) [26]. There was no significant heterogeneity in each of these analyses. One could argue that our limitation of including only attentional bias data to supraliminally presented sensory pain words was too restrictive. However, further analyses, which are not reported here but available on request, did not reveal any different results with less restrictive or other sets of data. Indeed, there were no significant effects of individual differences for subliminally presented sensory pain words, for subliminally presented affective pain words, for supraliminally presented affective pain words, for the combination of sub- and supraliminally presented sensory pain words, and for the combination of sub- and supraliminally presented affective words.

The effect of Individual differences as categorical variables. One could also argue that the approach to combine correlations as previously discussed is not adequate because it does not take into account problems related to a restricted range of values on the individual variables in the studies [61]. This may well have occurred here. Patients are often selected via different procedures, and/or different settings. For example, in the study

of Asdmundson et al. (2005) 36 patients with chronic musculoskeletal pain were recruited from a pain rehabilitation program in one of three major hospitals [10]. The mean Beck Depression Inventory score is 19.88 (*SD*=9.27), which is within the range for a moderate risk for depression. Payne and colleagues (2005) recruited 17 women suffering from chronic dyspareunia via media advertisements and screening during a semi-structured telephone interview [115]. The mean Beck Depression Inventory score in that study is low (*M*=9.76, *SD*=4.56) in comparison with the study of Asmundson et al. (2005). To remediate this problem we categorized participants from each study according to a priori criteria into a low or a high scoring group for a measure.

Clinical cut-offs were readily available in manuals and/or research papers for the Beck Depression Inventory [15] (high group > 19; [17]), depression subscale of the Depression Anxiety Stress Scales - short form and Depression Anxiety Stress Scales (high group > 13; [84]), Zung [168] (high group > 59; [111]), depression subscale of the Hospital Anxiety and Depression Scale [167] (high group > 10; [166]), anxiety subscale of the Hospital Anxiety and Depression Scale (high group > 10; [166]), anxiety subscale of the Depression Anxiety Stress Scales - short form and Depression Anxiety Stress Scales (high group > 9; [84]) Beck Anxiety Inventory (high group > 15; [16]), Visual Analogue Scale- intensity (high group > 5.4; [27]). For those measures without clinical cut-offs, we used a statistical criterion. We categorized participants in the high group whenever their score was one standard deviation above the mean score. In order to obtain sufficient accuracy, whenever needed, we pooled the means and standard deviations from manuals and/or publications until the standard error of mean was less than 1% of the scale range [31]. For measures that were pain-related (including the ASI) we pooled means and standard deviations from samples that consisted of individuals with chronic pain. That way statistical cut-offs were calculated for the pain severity subscale of the Multidimensional Pain Inventory [68] (high group > 5.510, *M*=4.257, *SD*=1.253, *n*=6532, *k*=1; [132]), Pain Rating Index of the McGill Pain Questionnaire [99] (high group > 41.87, M_{pooled}=28.94, SD_{pooled}=12.93, *n*=8968, *k*=10; [42,54,55,87,88,143,144]), Short Form McGill Pain Questionnaire [100] (high group > 28.76, M_{pooled}=19.43, SD_{pooled}=9.33, *n*=1371, *k*=6; [28,29,36,86,90,164]), Present Pain Index of the McGill Pain Questionnaire and Short Form McGill Pain Questionnaire (high group > 3.95, M_{pooled}=2.82, *SD*=1.125, *n*=1054, *k*=4; [28,29,86,90]), Pain Anxiety Symptoms Scale [95] (high group > 114, M_{pooled}=78.98, SD_{pooled}=34.68, *n*=1322, *k*=5; [124,158,169]), fear of pain subscale of the Pain Anxiety Symptoms Scale (high group > 26.26, M_{pooled}=16.10, SD_{pooled}=10.16,

n=1238, *k*=6; [66,124,169]), Anxiety Sensitivity Index (High group > 32.875; M_{pooled}=20.53, SD_{pooled}=12.34, *n*=1189, *k*=14; [5,7,8,10,19,41,56,82,94,115,118,134,138,169]), Tampa Scale of Kinesiophobia [70] (High group > 47.46; M_{pooled}=39.18, SD_{pooled}=8.27, *n*=4388, *k*=9; [36,112,130]), Pain Catstrophizing Scale[142] (High group > 37.19; M_{pooled}=24.69, SD_{pooled}=12.50, *n*=1189, *k*=14; [3,19,33,36,37,43,88,102,121,124,149,158,163]), catastrophizing scale of the Pain-Related Self Statements Scale [51] (High group > 3.81, M_{pooled}=2.67, SD_{pooled}=1.14, *n*=4264, *k*=2; [51,112]), Fear of Pain Questionnaire –III [97] (High group > 92.02, M_{pooled}=70.81, SD_{pooled}=21.21, *n*=343, *k*=4; [41,57,169]) . For measures that were not pain-related we pooled means and standard deviations from samples that consisted of individuals from the general population. There was only one exception to this rule, the MPI-AF subscale for which only samples with chronic pain were available. Statistical cut-offs were calculated for the trait subscale of the State-Trait Anxiety Inventory [139] (high group > 44.06, M_{pooled}=34.87, SD_{pooled}=9.20, *n*=1838, *k*=2; [140]), state subscale of the State-Trait Anxiety Inventory (high group > 46.04, M_{pooled}=35.59, SD_{pooled}=10.45, *n*=1838, *k*=2; [140]), affective distress subscale of the Multidimensional Pain Inventory [68] (high group > 4.76, *M*=3.42, *SD*=1.34, *n*=6532, *k*=1; [132]).

A mixed model meta-analysis was performed on the effect sizes (*d*) for the low and high scoring groups. The effect sizes of the low group and the high group were significant for all constructs, except for trait anxiety. The most important question, however, is whether the effect size differs between the low and the high group The between-group analyses did not reveal any significant effect between the low and the high scoring group for pain severity, $Q(1) = 0.023$, for pain-related fear, $Q(1)=0.322$, for state anxiety, $Q(1)=0.099$, for depression, $Q(1)=0.326$, and for trait anxiety, $Q(1)=0.260$ (See Supplementary table 4).

Interim summary. Although we may expect that individual differences in pain severity, pain-related fear, state anxiety, depressive mood and trait anxiety affect attentional bias towards supraliminally presented sensory pain words, no such effect was revealed.

3.9. Attentional bias to signals of pain

As indicated earlier, there were a number of studies that investigated attentional bias towards signals of impending pain, instead of attentional bias towards symbolic representations of pain. We already indicated that the effect size of the attentional bias

towards signals of pain was substantially different from the effect sizes of attentional bias towards symbolic representations of pain (e.g. words, pictures).

There were four studies with a total of 177 healthy volunteers investigating whether an attentional bias towards signals of impeding pain exist. All studies used the modified spatial cueing paradigm. All used a classical conditioning procedure in which one cue became predictive of impending pain, and another cue was never followed by pain. Attentional bias towards these cues was investigated. The cue predictive of pain was considered as pain-related information, the other cue as neutral information.

The effect size for the attentional bias towards signals of pain was significant (d= 0.673, 95%CI [0.379: 0.967], p<.001). There are no control groups that allow a comparison between pain and control group. There was substantial heterogeneity in the effect size of the attentional bias (Q(3)=8.655, p<.05). Unfortunately, we were unable to perform a moderator analysis with the procedural characteristics, as these were highly similar to all studies. All studies used a modified spatial cueing task in which pain-related and neutral trials were randomly presented. Stimulus exposure was always supraliminal, and never exceeded 500 ms. An exploration of the effects of individual differences was possible. All studies had a measure of pain-related fear (Pain Catastrophizing Scale) and one study had a measure of trait anxiety (STAI-trait). An analysis on the correlation coefficients did not reveal significant correlation coefficients (pain-related fear: r=-.007, 95% CI [-0.158: 0.145], n=177, k=4; Trait anxiety: r=-0.041, 95% CI [-0.316: 0.240], n=50, k=1). As the samples in these studies may be considered homogeneous, it is unlikely that the problem of range restriction is an issue for these analyses.

Interim summary. An attentional bias towards signals of pain is present. Although there is systematic variation between the effect sizes of the studies, we were unable to identify possible sources. The studies did not differ in their procedural characteristics, and differences between participants in pain-related fear and trait anxiety did not affect the extent of the attentional bias.

4. GENERAL DISCUSSION

Attentional bias towards pain-related information is not easy to identify, generate, or replicate. It is not a robust phenomenon. This conclusion supports the view of Dear and colleagues (2011) who stated that "the literature regarding pain-related attentional biases is currently marked by considerable inconsistency", and Haggman and colleagues (2010): "findings for attentional biases in pain patients are mixed". Our results can be

readily summarized. First, chronic pain patients show an attentional bias towards pain-related words or pictures, but this effect is small and no different from controls. Second, there was no evidence for attentional bias towards pain-related words and pictures in acute, procedural, and experimental pain. Third, healthy volunteers show an attentional bias towards signals of impending pain. Fourth, the type of pain-related information and its exposure time affected attentional bias in chronic pain. Fifth, individual differences in pain severity, pain-related fear, anxiety, depression and trait anxiety did not affect attentional bias in chronic pain.

Meta-analyzing data across available studies revealed that an attentional bias towards pain-related information in chronic pain is less robust (i.e., hard to produce and replicate), and of a smaller magnitude than what is commonly observed in patients with phobia and anxiety disorders (d=0.45) [11]. This conclusion is at odds with previous meta-analyses on this topic [129,135]. Differences may relate to the fact that in recent years many studies on attentional bias were published that were not included in previous analyses (e.g. [24,160]), or because our meta-analysis includes variables not previously considered (e.g. [73,89,109]). There are however findings that are similar, or that can be considered as further precision or extension. These relate to the results of our moderator analyses.

The type of pain-related information affected attentional bias in chronic pain. We found an attentional bias towards words that reflect the sensory characteristics of pain, but the size of the effect was small. These results extend the meta-analysis of Schoth and colleagues (2012), which did not address the issue of stimulus material, but are in line with the results of an early meta-analysis including only modified Stroop tasks [129]. Unexpectedly, we did not observe an attentional bias towards words that reflect the affective characteristics of pain. This is different from the conclusion of the meta-analysis of Roelofs and colleagues (2002). Notwithstanding some notable differences, it is clear from their report that the bias towards affective pain words was not strong, and was mainly driven by the large effect in one study [116], which lacked statistical information to calculate our effect size measure. Overall, our results are in line with research demonstrating that patients of various disorders display an attentional bias towards information that is specifically related to the content of their concerns [21,25,50,117,165]. It may be that sensory pain words are more specifically related to these concerns than affective pain words.

Another moderator was the exposure time of the stimulus material. Patients with chronic pain showed only an attentional bias when sensory words were supraliminally presented. When these words were subliminally presented, patients directed attention away, but this effect was no different from controls. These observations are in contrast with attentional bias in fear and anxiety disorders, which is found during both subliminal and supraliminal presentations [11]. Attentional bias in chronic pain may not rely on pre-attentive processes, which in the fear and anxiety literature are hypothesized to play a key role in the fast detection of threat in the environment [91]. In chronic pain it may be that conscious and elaborative processes are critical for attentional bias to emerge. The phenomenon may bear similarities to attentional bias in depression or dysphoria. Indeed, research on dysphoria and depression report bias with long rather than short exposure durations, indicating a dwelling of attention upon threat-related information and a difficulty disengaging attention from it [71,72,78]. In line with this view, Schoth and colleagues (2012) proposed that attentional bias in chronic pain is characterized not by the initial orienting of attention, but by the maintenance of attention on pain-related information. It is hypothesized that repetitive negative thinking about chronic pain and related problems, (i.e., worrying) maintains attention on pain-related information. Although plausible, this view awaits empirical corroboration. Our meta-analysis did not reveal that exposure durations that are indicative of initial orienting (<500ms) lead to a smaller bias than exposure durations indicative of maintenance.

Pain patients are heterogeneous and vary widely in terms of cognition, affect and behaviour. It may be that attentional bias is only to be found in some patients. In line with this reasoning, some models have formulated specific hypotheses. According to the fear-avoidance model, pain catastrophizing and pain-related fear lead to avoidance behaviour and attentional bias [34,76,157]. According to the misdirected problem solving model, worrying about pain and the resulting attempts to solve pain, fuel hypervigilance for pain and related information [1,46]. According to the schema enmeshment model, all patients display an attentional bias towards the sensory characteristics, but only those who are affectively distressed will bias their attention towards affective and illness-related information [120]. According to models of psychopathology [11,92,103], we may expect an attentional bias especially in those with a disposition to experience anxiety. To substantiate these ideas we have taken huge efforts to explore the effects of individual differences in pain severity, pain-related fear, depression, anxiety and trait anxiety on attentional bias. The results are perplexing and disappointing. We did not find evidence

for any of these hypotheses. The correlations were of a negligible effect size. Also categorizing patients in high or low groups did not reveal any effects. We may speculate about the many reasons for these null findings. Most likely, the problem relates to the fact that the current paradigms suffer from an unsatisfactory level of reliability according to psychometric standards. This has been reported in pain research [39], but also in other areas of psychology [74,133]. This critical, and yet unresolved problem prevents the use of these paradigms for clinical purposes, and limits their utility for exploring the role of individual differences [133].

Many studies in chronic pain use linguistic or pictorial stimuli that are only indirectly related to pain. Pearce and Morley (1989) were the first to use words that reflect the sensory and affective quality of pain, and many have adopted that stimulus material. However, these authors only aimed to validate the distinction between the sensory and affective pain scales of the McGill Pain Questionnaire. There is no reason to persist with this stimulus material. The use of linguistic stimuli is unfortunate as there are doubts about their capacity to automatically activate pain memory/schemata in patients, an assumption in many models [25,154]. In attempting to overcome this problem, researchers have started to use pictures as stimuli [38,134]. Although pictures may be more ecologically valid than words, it is not yet clear whether they are better suited to activate pain schemata/memories. Pain-related pictures often depict complex visual scenes (e.g. pictures of a man lifting a heavy bag) that are probably not immediately appraised as pain-related. When researchers want to pursue the use of words or pictures, we strongly recommend the documentation of how their stimuli are associated with pain (schemata/memory). Techniques are available [48], but have seldom been used [49]. Another avenue is to develop somatosensory versions of attentional bias paradigms. Ultimately, attentional bias in most models is discussed hand in hand with a selective processing of pain or associated stimuli at the cost of other environmental information [35]. One such variant was included in our meta-analysis, and, indeed, we observed an attentional bias towards signals of impending pain of medium effect size [152]. However, more work needs to be done in order to adapt these paradigms for use with chronic pain. Important challenges will be to make these paradigms relevant for the pain of patients, and to achieve an acceptable level of reliability in order to investigate the role of individual differences.

There are limitations to this meta-analysis. First, we need to be aware that ‘no evidence for an effect’ is not the same as ‘evidence for no effect’. There are some areas,

in which analyses are likely to be statistically underpowered. There are not many studies with procedural pain, the modified spatial cuing paradigm, pictures, or long exposure durations. Second, for the sake of parsimony and clarity of communication, we reported only the main analyses. Further analyses are possible. An exploration of the role of individual differences in the control groups or in other types of pain-related information might be considered. Third, publication bias is always a concern: it is possible that the reported effect sizes are still overestimated. Fourth, we limited our meta-analyses to three paradigms. Other behavioural paradigms have been developed in psychopathology [146,159,162] and some have been recently applied in pain [59,113]. Fifth, behavioural paradigms have limitations. Attentional biases are inferred based upon reaction times, which may be too noisy (i.e., overexposed to error variance) in some samples [148,153]. The current paradigms also provide only a snapshot of the timing of bias. Eye movement registrations may be an alternative [79,104,159].

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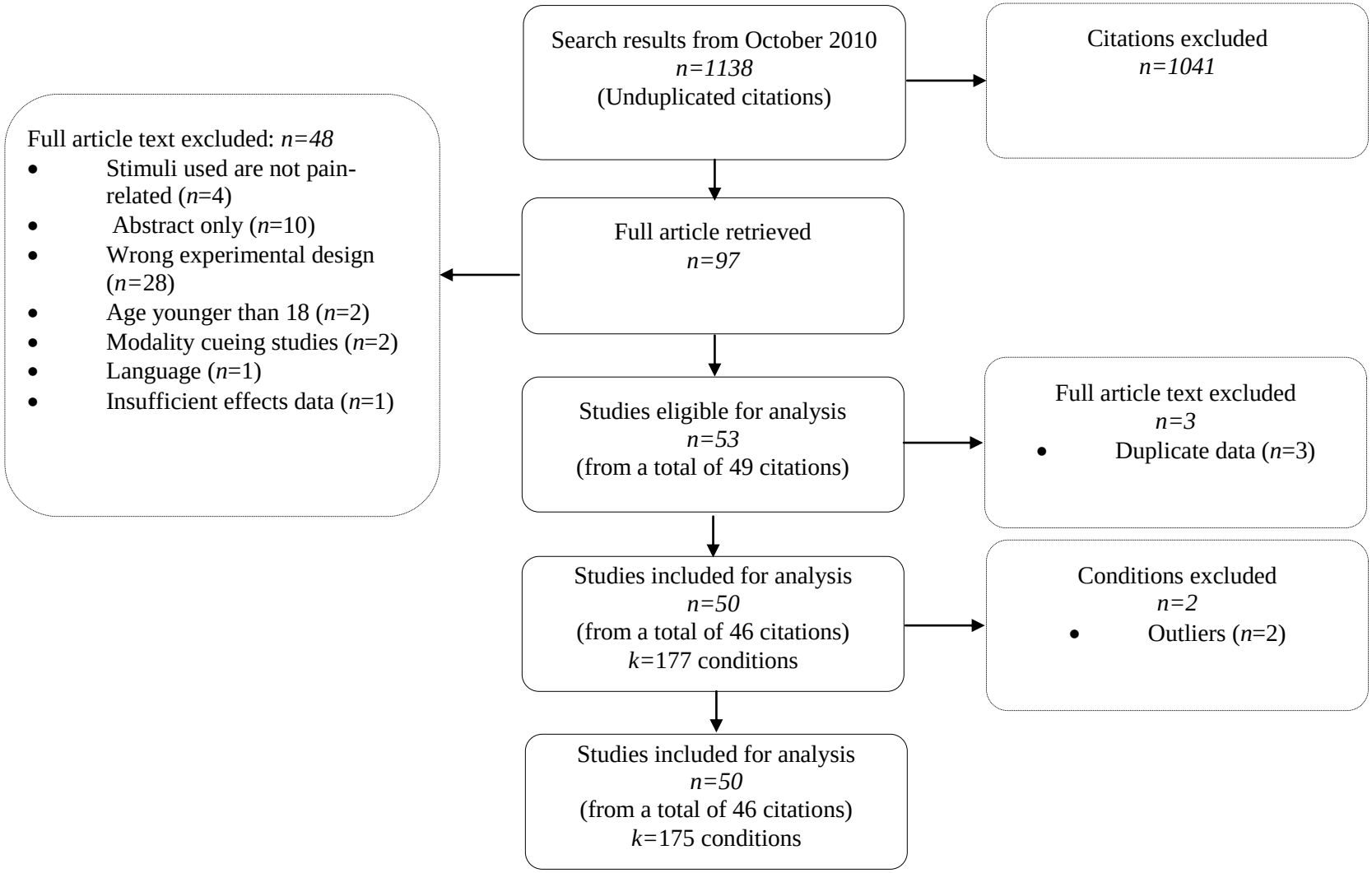

Figure 1: Flowchart for meta-analysis

Table 1

Table 1 provides the percentage of studies that fulfils each of the external/ internal validity criteria as a function of Attentional Bias Paradigm and Group. Also provided are mean internal and external validity scores (and *SD*) as a function of Paradigm and Group (range: 0 = none of the criteria are on average fulfilled; 1 = all criteria are on average fulfilled).

	kappa	Paradigm			Group		Overall
		Stroop	Dot-probe	Spatial cueing	Pain group	Control group	
Description of eligibility criteria (in terms of age, sex, diagnosis….)	.79	46.7%	76.9%	100.0%	63%	63.6%	62.1%
Description of the demographics of participants	.74	68.2%	78.3%	83.3%	65.8%	76.5%	74.0%
Description of the pain experience in the pain group	.78	81.3%	94.1%	83.3%	86.8%	81.8%	86.8%
Description of the pain experience in the control group	.80	26.3%	46.7%	50.0%	43,5%	35.5%	34.3%
Description of the recruitment procedure	.88	50.0%	47.8%	100.0%	60.5%	41.2%	56%
Description of the setting and/or location of the study of participants in the pain group	.73	93.8%	94,1%	100.0%	94.7%	100.0%	94.7%
Description of the setting and/or location of the study of participants in the control group	.78	78.9%	93.3%	100.0%	78.3%	88.2%	85.7%
Description of the data cleaning, and its criteria	.79	45.5%	65.2%	100.0%	57.9%	58.8%	60%
Mean external validity score (*SD*)		**0.61 (0.23)**	**0.73 (0.16)**	**0.94 (0.10)**	**0.72 (0.24)**	**0.66 (0.21)**	**0.70 (0.21)**
Relevance of the pain-related information (min. score2)	.70	31.8%	26.1%	66.7%	47.4%	26.5%	36%
Non pain-related information is adequately matched to pain-related information (min. score2)	.63	54.5%	82.6%	33.3%	63.2%	61.8%	64%
Participants engagement with the task	.88	45.5%	52.2%	100.0%	52.6%	52.9%	56%
Mean internal validity sore (*SD*)		**0.52 (0.23)**	**0.58 (0.21)**	**0.74 (0.17)**	**0.57 (0.23)**	**0.55 (0.23)**	**0.57 (0.22)**

Table 2

The combined within-group effect sizes (Cohen's *d*, 95¨% confidence interval) for the chronic pain groups and the control groups, and the difference between these effects sizes ($Q_{Between}$) between the two groups as a function of procedural characteristics.

	Chronic Pain Groups			**Control Groups**			
	k	*n*	*d* 95% CI [LL:UL]	k	n	*d* 95% CI [LL:UL]	$Q_{Between}$
Paradigm							
Dot probe task	12	734	0.091 [-0.017:0.199]	15	701	0.003 [-0.081:0.087]	1.572
Modified Stroop	12	272	0.168* [0.009:0.326]	19	666	0.181* [0.040:0.323]	0.016
Modified Spatial Cueing paradigm	2	53	0.222 [-0.052:0.495]	2	60	-0.192 [-0.590:0.206]	2.823
Modified Stroop task							
Blocked	4	80	0.341* [0.045:0.637]	6	142	0.404** [0.102:0.706]	0.085
Random	8	192	0.087 [-0.086:0.259]	11	404	0.037 [-0.122: 0.196]	0.173
Type of Stimuli							
Pictures	3	236	0.045 [-0.204:0.293]	3	111	0.086 [-0.255:0.427]	0.038
Words	23	832	0.148** [0.059:0.236]	34	1377	0.086 [-0.003:0.175]	0.922
Stimulus Exposure							
Subliminal	2	69	-0.174 [-0.413:0.065]	4	176	-0.258 [-0.577:0.061]	0.170
Supraliminal	25	1023	0.149** [0.058:0.239]	35	1398	0.088 [-0.000:0.177]	0.875
< 500 ms	3	364	0.082 [-0.215:0.380]	3	141	-0.316** [-0.485:-0.146]	5.183*
500 ms -1000 ms	12	597	0.077 (0.042) [-0.04:0.158]	15	647	0.064 [-0.026:0.153]	0.047
> 1000 ms	3	72	0.723*** [0.462:0.985]	4	127	-0.150 [-0.478:0.178]	16.658**
Type of Pain-related information							
Sensory quality	18	731	0.316*** [0.205:0.427]	21	911	0.016 [-0.064:0.095]	18.655***
Affective quality	11	554	0.083 [-0.015:0.182]	8	226	0.084 [-0.113:0.281]	0.424
Antecedents	7	186	0.160* [0.014:0.306]	11	467	0.183 [-0.005:0.371]	0.034
Consequences	9	665	-0.065 [-0.142:0.011]	5	161	-0.156 [-0.412:0.101]	0.439

Paradigm only with sensory pain words							
Dot probe task	10	546	0.292*** [0.162:0.422]	11	581	-0.018 [-0.115:0.080]	13.983**
Modified Stroop task	7	168	0.368* [0.084:0.653]	9	299	0.091 [-0.041:0.223]	3.018
Modified spatial cueing oaradigm	2	53	0.222 [-0.052:0.495]	2	60	-0.192 [-0.590:0.206]	2.823
Modified Stroop task only with sensory pain words							
Blocked	3	57	0.600*** [0.316:0.884]	3	57	0.246 [-0.084:0.576]	2.545
Random	4	111	0.211 [-0.145:0.568	6	242	0.055 [-0.071:0.182]	0.651
Stimulus Exposure only with sensory pain words							
Subliminal	2	69	-0.274* [-0.514:-0.033]	3	143	-0.120 [-0.285:0.044]	1.065
Supraliminal	18	731	0.341*** [0.238:0.445]	21	931	0.013 [-0.073:0.098]	23.205***
< 500 ms	2	53	0.240 [-0.034:0.514]	3	141	-0.316*** [-0.485:-0.146]	11.433***
500 – 1000 ms	11	579	0.247***[0.131:0.364]	11	527	0.058 [-0.046:0.162]	5.647*
> 1000 ms	2	113	0.698*** [0.269:1.127]	2	58	-0.225 [-0.720:0.271]	7.615**

Note: 95% CI [LL,UL] = 95% Confidence Interval [Lower Limit, Upper Limit]; ***= $p < .001$; **= $p < .01$; * = $p < .05$.

Supplementary table 3

The most frequently used measures of individual differences between chronic pain patients, and the combined within-group correlation coefficient between the individual differences and attentional bias towards supraliminally sensory pain words in chronic pain patients.

	k	***n***	**Name of the measure (acronym)**	**Author(s)**	**Primary content of measure**	**Number of items**	**Response scale**	**Range**	***r*, 95% CI [LL:UL]**	**Studies using instrument**
Pain Severity	**10**	**481**							**-0.043 [-0.134:0.050]**	
	7	265	Pain Intensity Visual Analogue Scale (Intensity VAS)		Pain intensity	1	0 = no pain 10 = worst possible pain **	0 - 10	-0.031 [-0.155:0.094]	[5,7,57*,82,125,136,138]
	2	198	Multidimensional Pain Inventory: pain severity subscale (MPI-PS)	Kerns et al., 1985 [68]	Pain intensity	3	0 – 6	0 – 6	-0.049 [-0.189:0.092]	[10,41]
Pain-related fear	**10**	**438**							**0.031 [-0.098:0.158]**	
	4	283	Tampa Scale for Kinesiophobia (TSK)	Kori et al., 1990 [70]	Fear of movement and (re)injury during physical activity	17	1 = strongly disagree - 4 = strongly agree	17 - 68	-0.048 [-0.325:0.237]	[41,125,57**]
	3	95	Fear scale Pain Anxiety Symptoms Scale (PASS-fear of pain)	McCracken et al., 1992 [95]	Fearful appraisal of pain	10	0= never - 5= always	0 - 50	0.017 [-0.192:0.225]	[5,10,138]
	1	156	Pain Related Self Statements Scale: catastrophizing scale (PRSS)	Flor et al., 1993 [51]		9	0 = almost never - 5 = almost always	0 – 5	-0.104 [-0.257:0.054]	[41]

	3	267	Fear of pain Questionnaire-III (FPQ-III)	McNeil & Rainwater, 1998 [97]	Fear of painful situations:	30	1 = not at all - 5 = extreme	30 – 150	0.038 [-0.084:0.158]	[41,57**]
	7	318	Anxiety Sensitivity Scale (ASI)	Reiss et al., 1986 [123]	fear of anxiety symptoms including thoughts and somatic sensations.	16	0 = very little -4 = very much	0 - 64	0.065 [-0.110:0.236]	[5,7,10,41,82, 115,138]
State anxiety	**13**	**574**							**-0.017 [-0.101:0.068]**	
	3	153	Anxiety subscale Hospital and Anxiety Subscale (HADS-A)	Zigmond & Snaith, 1983 [167]	Anxiety during the last week	7	0= not at all - 3= most of the time	0 - 21	-0.111 [-0.268:0.052]	[24,89,136]
	1	163	Anxiety subscale of the Depression Anxiety Stress Scales 42 (DASS-A)	Lovibond & Lovibond, 1995 [84]	Anxiety during the past week	14	0 = did not apply to me at all - 3 = applied to me very much, or most of the time	0 - 42	-0.033 [-0.186:0.121]	[41]
	7	168	State subscale of the State-trait Anxiety Inventory for Adults (STAI-S)	Spielberger et al., 1970 [139]	Anxiety at this moment	20	1 = not at all - 4 = very much	20 - 80	0.014 [-0.147:0.173]	[2,5,7,10,82, 115,138]
Depression	**14**	**624**							**-0.051 [-0.133:0.031]**	
	3	153	Depression subscale of the Hospital Anxiety and Depression Subscale (HADS-	Zigmond & Snaith, 1983 [167]	Depressive mood during the last week	7	0 = not at all - 3 = most of the time	0 - 21	-0.064 [-0.224:0.099]	[24,89,136]

			D)							
	1	163	Depression subscale of the Depression Anxiety Stress Scales (DASS-D)	Lovibond & Lovibond, 1995 [84]	Depressive mood during the past week	14	0 = Did not apply to me at all - 3 = Applied to me very much, or most of the time	0 - 42	-0.049 [-0.201:0.106]	[41]
	7	170	Beck depression Inventory (BDI)	Beck & Steer, 1987 [15]	Depressive mood during the past two weeks	21	0 - 3	0 - 63	-0.063 [-0.243:0.122]	[2,5,7,10,82, 115,138]
Trait anxiety	**6**	**150**							**0.013 [-0.165:0.190]**	
	6	150	Trait subscale of the State-trait Anxiety Inventory for Adults (STAI-T)	Spielberger et al., 1970 [139]		20	1 = Almost never - 4 = Almost always	20 - 80	0.013 [-0.165:0.190]	[5,7,10,82,115 ,138]

Note. 95% CI [LL:UL] = 95% Confidence Interval [Lower Limit, Upper Limit]; * = only one group is included; **= both groups are included; *** = 0 - 100 VAS-Scales were rescaled to 0 - 10 VAS-scales.

Supplementary table 4

The combined within-group effect sizes (Cohen's *d*, 95¨% confidence interval) for chronic pain patients scoring low and high on pain severity, pain-related fear, depression, state anxiety, and trait anxiety, and the difference in effect sizes ($Q_{Between}$) between the two groups.

	Name of the measure (acronym)	Pooled *M* (*SD*) of articles included in meta-analysis	Cut-off	Low Group			High Group			high vs. low Group ($Q_{between}$)
				k	***n***	***d* 95% CI [LL: UL]**	***k***	**n**	***d* 95% CI [LL: UL]**	
Pain Severity				**11**	**353**	**0.276** [0.090: 0.463]**	**9**	**129**	**0.256** [0.078: 0.435]**	**0.023**
	Intensity VAS	4.711 (2.638)	>5.40	8	154	0.230* [0.015: 0.444]	8	115	0.297*** [0.107: 0.486]	0.212
	MPI-PS	4.044 (1.113)	>5.51	2	183	0.243 [-0.251: 0.737]	1	14	-0.054 [-0.578: 0.471]	0,653
Pain-related fear				**10**	**352**	**0.271** [0.094: 0.448]**	**7**	**74**	**0.357** [0.119: 0.596]**	**0.322**
	TSK	39.890 (8.608)	>47.46	4	223	0.360*** [0.141: 0.579]	4	60	0.351* [0.044: 0.659]	0.002
	PASS-fear of pain	15.973 (8.031)	>26.26	3	82	0.155 [-0.141: 0.452]	2	12	0.487 [-0.115: 1.089]	0.939
	PRSS	2.603 (1.080)	>3.81	1	136	0.443*** [0.267: 0.619]	1	20	0.073 [-0.365: 0.512]	2.347
	FPQ-III	69.820 (19.685)	>92.02	3	234	0.447*** [0.313: 0.582]	3	33	0.477** [0.113: 0.840]	0.022
	ASI	19.313 (11.372)	32.87	7	276	0.233* [0.014: 0.453]	5	40	0.475* [0.002: 0.948]	0.822
State anxiety				**13**	**383**	**0.318*** [0.205: 0.430]**	**13**	**191**	**0.285 [0.119: 0.452]**	**0.099**
	HADS-A	8.582 (4.220)	>10	3	109	0.257** [0.066: 0.449]	3	44	0.098 [-0.236: 0.432]	0.657

	DASS-A	8.828 (7.890)	>9	1	102	0.458*** [0.254: 0.662]	1	61	0.350** [0.091: 0.608]	0.412
	STAI-S	42.972 (9.141)	>46.04	7	110	0.211 [-0.025: 0.448]	7	58	0.288 [-0.038: 0.615]	0.140
Depression				**14**	**458**	**0.315*** [0.200: 0.430]**	**11**	**149**	**0.256** [0.091: 0.422]**	**0.326**
	HADS-D	5.301 (3.138)	>10	3	138	0.221* [0.051: 0.390]	2	14	0.190 [-0.355: 0.736]	0.011
	DASS-D	14.963 (12.386)	>13	1	90	0.464*** [0.246: 0.681]	1	73	0.367** [0.130: 0.604]	0.346
	BDI	13.133 (7.638)	>19	7	140	0.289* [0.060: 0.518]	5	29	-0.043 [-0.414: 0.328]	
Trait anxiety				**6**	**94**	**0.164 [-0.076: 0.405]**	**6**	**56**	**0.267 [-0.047: 0.582]**	**0.260**
	STAI-T	41.864 (8.946)	>44.06	6	94	0.164 [-0.076: 0.405]	6	56	0.267 [-0.047: 0.582]	0.260

Note. 95% CI [LL:UL] = 95% Confidence Interval [Lower Limit, Upper Limit]; VAS = Visual Analogue Scale; MPI-PS = Multidimensional Pain Inventory – Pain severity subscale; TSK = Tampa Scale of Kinesiophobia; PASS-fear of pain = Pain Anxiety Symptoms Scale-fear of pain subscale; PRSS = Pain-Related Self Statements Scale ; FPQ-III = Fear of Pain Questionnaire; ASI = Anxiety Sensitivity Index; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale – depression subscale; BDI = Beck Depression Inventory; STAI-T = State-Trait Anxiety Inventory – trait subscale; STAI-S = State-Trait Anxiety Inventory – State subscale; DASS-A = Depression Anxiety Stress Scales – anxiety subscale; DASS-D = Depression Anxiety Stress Scales – depression subscale; *** = $p < .001$; ** = $p < .01$; * = $p < .05$.